

time.²⁻⁴ This apparent paradoxical effect, however, is not generally appreciated because the dosage requirements of most other drugs are increased in thyrotoxicosis as a result of increased degradation. Warfarin exerts its anticoagulant action by interfering with the activation of the four vitamin K-dependent clotting factors, II, VII, IX, and X, through the inhibition of vitamin K epoxide reductase. In thyrotoxicosis, the metabolic clearance rate of some of these factors is increased, and the concentration of factor II is depressed.^{4,5} Thus, less warfarin would be required to prolong the prothrombin time in patients with thyrotoxicosis. In our patient, sensitivity to warfarin, which we have expressed as the quotient of INR and warfarin dose, increased abruptly when the patient first became aware of symptoms that, in retrospect, were in all likelihood due to the emergence of amiodarone-induced thyrotoxicosis. Return to the euthyroid state was accompanied by a decrease in sensitivity to warfarin.

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Persistent Hiccups Induced by Dexamethasone

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HICCUPS OR SINGULTUS are transient events experienced occasionally by most people. They are usually benign and of brief duration, but may become persistent. Although the cause of most episodes is never determined, many known associated conditions have been identified, including medications. We present a case of hiccups induced by the administration of dexamethasone.

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Report of a Case

The patient, a 30-year-old man with no relevant medical history, presented with coffee-ground emesis on the day of admission and persistent hiccups for two days. He had recently been evaluated by a dermatologist in Mexico and had received 16 mg of dexamethasone intravenously for "allergic skin lesions." Unfortunately, no further information was available. He denied prior intake of any medications, alcohol, or tobacco.

A physical examination showed persistent hiccups at a rate of 6 to 9 per minute, mild epigastric tenderness, and heme-positive stools. Multiple circumscribed papular skin lesions were seen over the flexor surface of the upper extremities, consistent with urticaria. Laboratory evaluation revealed a leukocyte count of 17.27×10^9 per liter with a normal differential cell count, a hemoglobin level of 158 grams per liter, and a hematocrit of 0.45. The results of electrolyte tests, liver function tests, and coagulation studies were normal.

Esophagogastroduodenoscopy revealed erosive esophagitis and gastritis. The following techniques were attempted unsuccessfully to terminate hiccups in the patient: Valsalva maneuver, stimulation of the pharynx with a cotton-tipped swab, and drinking water. The patient continued to have hiccups that also failed to respond to treatment with chlorpromazine.

The patient's hiccups resolved four days after the initial dexamethasone injection. Because dexamethasone was suspected as the cause of hiccups, the patient was offered a challenge test. The benefits and risks were explained to him, specifically the identification of a possibly avoidable drug side effect. After his authorization, the same dose of dexamethasone was administered intravenously one week after his discharge from the hospital. His hiccups reappeared within two hours and disappeared after 36 hours.

Discussion

Hiccups are involuntary contractions of the diaphragm, terminated by the abrupt closure of the glottis. Transient hiccup episodes can last as long as 48 hours. When an episode continues for more than 48 hours, it is termed persistent. Hiccups lasting longer than one month are considered intractable.¹ Transient hiccups occur equally in both sexes, but persistent and intractable hiccups occur more frequently in men.² Hiccups serve no physiologic function. The physiologic mechanism of hiccups is thought to result from the stimulation of one or more of the three components of the hiccup reflex arc, the afferent, central, and efferent limbs.³ The afferent limb comprises the phrenic and vagus nerves and the sympathetic chain from thoracic segments T6 to T12. The central connection between the afferent and efferent limbs is attributed to a nonspecific anatomic location between cervical segments C3 and C5. The efferent limb consists primarily of the phrenic nerve, in addition to the glottis, accessory respiratory muscles, and a complex interaction between the brainstem and midbrain areas, including the

respiratory center, phrenic nerve nuclei, medullary reticular formation, and hypothalamus.

The evaluation of persistent and intractable hiccups should focus on a thorough history, physical examination, and laboratory studies necessary to disclose possible underlying causes that could stimulate this reflex. Medications are not considered a common cause of hiccups. Souadjian and Cain² in their review of 220 cases of intractable hiccups do not report medications as a cause. Only three cases of dexamethasone-induced hiccups were reported in the literature.⁴⁻⁶ In another report, hiccups were associated with dexamethasone-cyclophosphamide pulse therapy.⁷ Persistent hiccups have also been reported with the use of methylprednisolone.⁸

The mechanism of corticosteroid-induced hiccups is not known. It has been proposed that corticosteroids may stimulate the hiccup reflex arc. Animal studies suggested that corticosteroids reduce the synaptic transmission threshold in the midbrain.⁹

The incidence of corticosteroid-associated hiccups is unknown. The few cases reported indicate either that the incidence is low or that the effect is so mild and self-limited that it goes unrecognized. Discontinuing the suspected drug usually results in the termination of hiccups. Recovery may take several hours to a few days.

Because corticosteroids are widely used in medicine, we would like to raise the level of awareness among clinicians of the association between corticosteroids and hiccups. A drug history should be carefully reviewed as a possible cause of hiccups. This will obviate the need for further unnecessary investigations.

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